Remarks

Rejections under 35 U.S.C. §112

Claims 51-53 and 55-62 stand rejected under 35 U.S.C. § 112 on the ground that the specification, while being enabling for treating malaria caused by *Plasmodium* parasite *P. falciparum* with triclosan, does not reasonably provide enablement for other inhibitors of fatty acid synthesis, such as other hydroxydiphenyl ethers disclosed in claims 51 and 53, and effective against the other three *Plasmodium* parasites that cause malaria, *P. vivax*, *P. ovale*, and *P. malariae*, or the addition of another known antimalarial agent with the inhibitors of fatty acid synthesis. For each of the following reasons, Applicant continues to maintain that the instant claims are enabled across their full scope based on the specification.

Firstly, while it is true that the specification only contains data showing the efficacy of triclosan, Applicant submits that the working examples are sufficient to demonstrate enablement of the claims. In particular, the specification shows that triclosan is effective against two different *Plasmodium* species, namely *P. falciparum* (*in vitro* data – see Examples 1 and 2, pp. 22-23, and the accompanying Figures 1 and 2) and *P. berghei* (*in vivo* data – see Example 3, p., 23, and the accompanying Figures 3 and 4). The *Plasmodium* species that cause malaria in humans do not cause malaria in rodents. Therefore it is not possible at this time to create a rodent animal model of malaria using *Plasmodium* species that cause malaria in humans. However, infection of rodents such as mice by the related *Plasmodium* species *P. berghei* is accepted in the art as being a useful *in vivo* animal model for malaria in humans. In particular, rodents infected with *P. berghei* become ill and die, and the survival of *P. berghei* –infected rodents is promoted by a variety of anti-malarial compounds that are also effective against *Plasmodium* that cause malaria in humans. Should the Examiner desire further evidence that infection of rodents with *P. berghei* is considered a useful animal model for malaria, such evidence can be obtained by examining the numerous articles retrieved by a search of Pubmed (www.pubmed.com) using the terms "berghei" and "anti-malarial" or by reviewing U.S. patents and patent applications that include data showing the efficacy of various alleged anti-malarial compounds against *P. berghei*. Thus Applicant submits that the specification shows evidence that triclosan inhibits growth of *two different* species of *Plasmodium* and thus is not limited to the administration of triclosan to treat malaria caused by *P. falciparum*.

Furthermore, as stated in MPEP 2164.02, even if the examples were limited to showing that triclosan treats malaria caused by *P. falciparum*, "The presence of only one working example *should never be the sole reason for rejecting claims as being broader than the enabling disclosure*...To make a valid rejection, one must evaluate all the facts and evidence and *state why one would not expect to be able to extrapolate that one example across the entire scope of the claims*." (emphasis added). Applicants submit that the Examiner has not explained why one of skill in the art would not expect to be able to extrapolate the example of triclosan across the entire scope of agents that inhibit fatty acid synthesis, particularly other hydroxydiphenyl ethers disclosed in claims 52 and 53. In essence, the Examiner's rejection is based solely on the fact that triclosan is the only compound shown to be effective, contrary to the guidance provided by MPEP 2164.02. In the absence of a reasonable explanation as to why the example of triclosan could be extrapolated across the entire scope of agents that inhibit fatty acid synthesis, particularly other hydroxydiphenyl ethers disclosed in claim 53, *there is no basis for requiring the claims to be limited to triclosan.*

Secondly, even if some experimentation is required to practice the claimed methods across their full scope, Applicant submits that such experimentation is merely routine or is described in detail in the specification and is therefore not "undue". The Federal Circuit has stated with respect to enablement that, " 'a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Methods for determining whether any particular compound, e.g., any particular hydroxydiphenyl ether disclosed in claims 51 and 53 and/or described elsewhere in the art (see, e.g., U.S. Pat. No. 3,629,477, cited previously by the Examiner) inhibits the growth of *P. falciparum* or *P. berghei* are described in the specification. Furthermore, additional methods for testing candidate anti-malarial compounds are known in the art, as will be evident to the Examiner. Therefore, Applicants submit that any experimentation required to carry out the instant claims across their full scope is by no means undue.

Thirdly, the fact that the instant claims with respect to treatment of malaria caused by *P. vivax*, *P. ovale*, and *P. malariae* meet the standard for enablement under 35 U.S.C. §112 is

further confirmed by the fact that the U.S. Patent and Trademark Office (USPTO) has previously issued patents with claims to compounds and methods of use thereof for the treatment of malaria, and the claims are not limited to malaria caused by *P. falciparum*, even though the data in the patents shows efficacy only in *in vitro* assays with *P. falciparum* and contains no data with respect to other *Plasmodium* species that cause malaria in humans. For example, U.S. Pat. No. 6,645,966, filed January 18, 2002, entitled, "Treatment of malaria with farnesyl protein transferase inhibitors" describes tests showing that certain compounds inhibited the growth of *Plasmodium falciparum in vitro* (see Example 11, paragraph bridging bottom of col. 68 and top of col. 69). Claim 1 is as follows: "A method for treating malaria comprising administering to a human in need of such treatment an effective amount of a compound selected from: ##STR115## ##STR116## ##STR117## ##STR118## ##STR119## ##STR120## ##STR121##." The patent contains only a single example showing activity of the compounds, namely an *in vitro Plasmodium falciparum* growth inhibition assay. Yet the claims are not limited to malaria caused by *P. falciparum*.

As noted above, infection of rodents such as mice by the related *Plasmodium* species *P. berghei* is accepted in the art as being an *in vivo* model for malaria. U.S. Pat. No. 6,143,756, filed May 13, 1999, entitled "Antimalarial activity of β-carboline alkaloids", describes the efficacy of manzamine A in inhibiting *P. berghei* in infected mice (Example 1) and the efficacy of manzamine A in inhibiting *P. falciparum in vitro* (Example 2). There is no data showing inhibition of *P. vivax*, *P. ovale*, and *P. malariae*. Claim 1 is as follows: "A method for treating or preventing malaria comprising administering to a subject a composition comprising Manzamine A." The claims are not limited to malaria caused by *P. falciparum*. Thus it is evident that the USPTO considered the combination of the *in vitro* data showing inhibition of *P. falciparum* and the *in vivo* data showing inhibition of *P. berghei* sufficient to establish enablement of claims that are not limited to *P. falciparum*.

The Examiner's attention is also drawn to U.S. Pat. No. 6,242,484, filed July 6, 1999, entitled "Hypoestoxides, derivatives and agonists thereof for use of antiparasitic agents" and U.S. Pat. No. 6,531,487, filed May 8, 2001, entitled "Indolo[2,1-b] quinazole-6, 12-dione antimalarial compounds and methods of treating malaria therewith" for additional examples.

Evidently in the case of each of the patents mentioned above the results obtained *in vitro* showing inhibition of *P. falciparum* and/or results obtained *in vivo* showing inhibition of *P.*

berghei in rodents were considered sufficient by the Patent Office to establish enablement and utility of claims directed to compounds and/or methods for the treatment of malaria.

Given that the claims are enabled for treating malaria by administering an antimalarial composition comprising a compound that is an inhibitor of fatty acid synthesis in the malaria parasite, e.g., a hydroxydiphenyl ether disclosed in claim 52 or 53, Applicant submits that a method of treating malaria wherein the composition further comprises one or more known antimalarial agents and a pharmaceutically acceptable adjuvant, diluent, or carrier, as recited in claim 55, is also enabled, absent evidence to the contrary. Note that the claims do not require that the composition of claim 55 or 56 is more effective than the composition of claim 52 or 53. There is no reason to believe that including a second antimalarial agent in a composition comprising an inhibitor of fatty acid synthesis would reduce the antimalarial activity of the inhibitor of fatty acid synthesis, and the Examiner has provided no evidence to suggest that this would be the case. Therefore, since claims 52 and 53 are enabled, Applicant submits that claim 55 and claim 56, which recites particular known antimalarial agents, are also enabled across their full scope.

The fact that claims to methods of treatment of malaria using a composition comprising an inhibitor of fatty acid synthesis and one or more known antimalarial agents meet the standard for enablement under 35 U.S.C. §112 is further confirmed by the fact that the USPTO has previously issued patents that contain claims to treating malaria using a particular compound in combination with a known antimalarial agent although the patents do not contain any data showing efficacy of the combination have issued. For example, U.S. Pat. No. 6,645,966, discussed above, contains the following claim 3: "A method for treating malaria comprising administering to a patient in need of such treatment an effective amount of a compound used in the method of claim 1, in combination with an effective amount of an additional antimalarial agent and/or an additional agent for reversing antimalarial resistance." The patent contains no data regarding combinations of the compound used in claim 1 and an additional antimalarial agent or an additional agent for reversing antimalarial resistance.

As further evidence that the instant claims are enabled across their full scope, enclosed herein is a Declaration of Dr. Namita Surolia, the inventor of the instantly claimed invention. As

described therein, it has been shown that four additional inhibitors of fatty acid synthesis, including three hydroxydiphenyl ethers that fall within the scope of claims 51 and 53, inhibit growth of *P. falciparum in vitro*. Two of the hydroxydiphenyl ethers have also been shown to inhibit *P. berghei in vivo* in mice. These results provide additional data demonstrating that the instant claims are enabled across their full scope.

For all of the above reasons, Applicant submits that all of the claims are enabled across their full scope. Withdrawal of the rejection is respectfully requested.

Applicant thanks the Examiner for his careful consideration of the present case. In view of the remarks presented herein and the enclosed Declaration, Applicant respectfully submits that the case is in condition for allowance. A Notice to that effect is earnestly requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial). Checks are enclosed to cover the fee for a Request for Continued Examination, a three (3) month extension of time, and an Information Disclosure Statement. Please charge any additional fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,

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